ORIGINAL RESEARCH

Reduced Long-Term Risk of Aortic Aneurysm and Aortic Dissection Among Individuals With Type 2 Diabetes Mellitus: A Nationwide Observational Study

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***Background*—**No studies have examined long-term risks for aortic aneurysm (AA) and aortic dissection (AD) or mortality after AA or AD hospitalization among patients with type 2 diabetes mellitus (T2DM).

***Methods and Results*—**In this observational cohort study, we linked data for patients with T2DM in the Swedish National Diabetes Register, and 5 individually matched population-based control subjects (CSs) without diabetes mellitus (on the basis of sex, age, and county), to other national databases to capture hospitalizations and death. We examined the risk of hospitalization for AA and AD, as well as mortality risk after AA and AD using Kaplan-Meier curves and Cox regression hazards models. Data on 448 319 patients with T2DM and 2 251 015 CSs were obtained between 1998 and 2015. Mean follow-up time was 7.0 years for the T2DM group and 7.2 years for the CS group. Patients with T2DM had a relative risk reduction of 28% (hazard ratio, 0.72; 95% confidence interval, 0.68–0.76; $P<0.0001$) for AA and a 47% relative risk reduction (hazard ratio, 0.53; 95% confidence interval, 0.42–0.65; $P<0.0001$) for AD compared with CSs. Patients with T2DM had a relative risk reduction of 12% (hazard ratio, 0.88; 95% confidence interval, 0.82–0.94; $P<0.0001$) for mortality after hospitalization for AA, and unaltered risk (hazard ratio, 1.07; 95% confidence interval, 0.85–1.34; $P=0.5859$) for mortality after AD, up to 2 years compared with CSs.

***Conclusions*—**Patients with T2DM had significantly reduced risks of AA and AD as well as reduced risk of mortality after hospitalization for AA, compared to CS. Data suggest that glycated cross-links in aortic tissue may play a protective role in the progression of aortic diseases among patients with T2DM. **(*J Am Heart Assoc*. 2018;7:e007618. DOI: 10.1161/JAHA.117.007618.)**

Key Words: aneurysm • aortic disease • cardiovascular disease • diabetes mellitus • mortality

Aortic diseases, categorized as aortic aneurysms (AAs)[1,2] or aortic dissections (ADs),[3,4] are not uncommon and are highly critical, despite modern diagnostic tools and surgical/endovascular treatment. In some cases, progressive enlargement of the aortic diameter leads to AA, which ruptures and creates a catastrophic cardiovascular event.[4,5] However, enlargement of the aorta is not always a good predictor of AD. A study conducted by the International Registry for Acute Aortic Dissections indicated that most ADs were not preceded by aortic dilatation.[4] Although the pathophysiological characteristics have been suggested to differ,[6] hypertension and smoking are risk factors for AA[2,7] and for AD,[5,6,8] whereas connective tissue disorders, such as Marfan syndrome and Ehler-Danlos syndrome, are risk factors for AD.[6,9] The same risk factors are known to be associated with increased risk of cardiovascular comorbidity and mortality.[10]

Diabetes mellitus (DM) affects hundreds of millions of people, with the vast majority having type 2 DM (T2DM).[11] T2DM is, even with intensive treatment, a major risk factor for cardiovascular disease and excess mortality compared with the general population.[10,12] However, previous studies have associated DM with reduced risk of AA[2,13–15] and AD.[8] Some

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Accompanying Tables S1, S2, and Figures S1 through S4 are available at http://jaha.ahajournals.org/content/7/3/e007618/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- The study included 448 319 patients with type 2 diabetes mellitus (T2DM) and 2 251 015 population-based control subjects without diabetes mellitus.
- Patients with T2DM had, compared with controls, a 28% relative risk reduction of hospitalization for aortic aneurysm and a 47% relative risk reduction of hospitalization for aortic dissection.
- Adjusted mortality rates after hospitalization for aortic aneurysm were 12% lower among patients with T2DM than controls.

What Are the Clinical Implications?

- T2DM may have protective effects against development of aortic disease (aortic aneurysm and aortic dissection) through structural changes in the aortic wall.
- T2DM may have positive short-term effects on survival after hospitalization for aortic aneurysm.

of the studies were limited in deciphering associations between T2DM and AA and AD because of their case-control design or the study population having been selected from a single center. Data about long-term real-life relationships between DM and AA and AD are scarce, and none has addressed the question of mortality risk after hospitalization for AA or AD.

The aim of this study was to explore the long-term association between T2DM and AA and AD in real life, as well as the risk of mortality after hospitalization for AA or AD. We used the Swedish National Diabetes Register (NDR) to identify patients with T2DM and compared them with control subjects (CSs) from the general population.

Methods

This nationwide, observational, longitudinal, explorative population-based matched cohort study included nearly 3 million Swedish subjects. The study was approved by the Ethics committee of the University of Gothenburg (Gothenburg, Sweden). All patients had given their informed consent to participate. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Individuals With T2DM and CSs

The NDR, founded in 1996, is an integral part of DM care in Sweden and serves as a nationwide quality assurance and improvement tool for care providers, covering most Swedish patients with DM aged ≥18 years.[16] It contains information about clinical characteristics, risk factors, DM-related complications, and treatments. Virtually all patients with DM who receive primary or specialist care are reported to the NDR.[17]

We used the epidemiological definition of T2DM: dietary treatment only or oral antihypoglycemic agents, or in patients diagnosed with DM at the age of ≥40 years taking insulin with or without oral antihypoglycemic agents.[18]

In this study, we included at baseline, patients with DM with initial entry in the NDR between 1998 and 2012. For every patient with T2DM, 5 CSs were randomly selected from the Swedish Total Population Register and matched for age, sex, and county.[19]

Databases and Procedures

Data were obtained from national databases and registries. The 12-digit personal identity number is unique to every Swedish inhabitant. Using the number, information from nationwide population-based databases can be linked. Thus, we could fully link data for patients with T2DM and CSs.

Besides the NDR, we used the Inpatient Register with nationwide data for primary and secondary discharge diagnoses and lengths of hospitalization since 1987[20]; the Prescribed Drug Register with complete information about filled prescriptions since 2005[21]; the longitudinal integration database for health insurance and job market studies (Statistics Sweden); and the Cause of Death Register with complete information on death causes and time of death.[22] The Swedish registers containing validated population-based data, The Inpatient Register, and the Cause of Death register are administered by the National Board of Health and Welfare (http://socialstyrelsen.se/english).[20]

Socioeconomic Characteristics

Socioeconomic characteristics at baseline were obtained by data linkage to the longitudinal integration database for health insurance and job market studies. Marital status was broken down into single, married, divorced, or widowed. Educational level was broken down into compulsory school (level 1), upper secondary school (level 2), and college/university (level 3). Native country was either Sweden or other.

Comorbidities and Drug Treatment at Baseline

Information about comorbidities and drug treatment at baseline was obtained by data linkage to the Inpatient Register and Prescribed Drug Register. The Inpatient Register uses *International Classification of Diseases* (*ICD*) codes, both revisions 9 and 10, for classification of diagnoses. The Prescribed Drug Register helped us define other drug treatment.

Comorbidities and drug treatment at baseline included the following: heart failure, atrial fibrillation, hypertension, coronary heart disease, and stroke. Acute myocardial infarction was defined as codes 410 (*ICD-9*) and I21 (*ICD-10*). Cardiovascular disease was defined as coronary heart disease and/or stroke before index date. At baseline, we also included Marfan and Ehler-Danlos syndromes, psychiatric disorders, dementia, cancer, renal complications, gastric bypass, and DM complications (hyperglycemia). Use of acetylsalicylic acid, lipid-lowering medications, and anticoagulation therapy was also included. For all *ICD* codes used in the study, refer to Table S1.[19]

Hypertension was defined as 3 filled prescriptions for antihypertensive medication for 1 year before index date. In Sweden, 1 prescription is equivalent to 3 months of continuous use of a drug. The most common antihypertensive medications in Sweden at the time of the study were as follows: angiotensin-converting enzyme inhibitors, diuretics, calcium channel blockers, angiotensin 2 blockers, α-1 receptor blockers, β blockers, and various combinations of the described medications. Use of lipid-lowering drugs and use of acetylsalicylic acid were defined in a similar manner.

Follow-Up and End Points

For the main analyses, all patients were studied from baseline until an end point, death or end of the study (May 31, 2015). The major primary end points were hospitalization for AA or AD and death. AA was defined as codes 441.1 to 441.7 and 441.9 (*ICD-9*), where 441.1, 441.3, 441.5, and 441.6 (*ICD-9*) were thoracic, abdominal, unspecified, and thoracoabdominal ruptured aneurysms, respectively; and codes I71.1 to I71.6 and I71.8 to I71.9 (*ICD-10*), where I71.1, I71.3, I71.5, and I71.8 (*ICD-10*) represented thoracic, abdominal, thoracoabdominal, and unspecified ruptured aneurysms, respectively. AD was defined as codes 441.0 to 441.3 (*ICD-9*) and I71.0 (*ICD-10*).

The other main end point was an analysis of death after hospitalization for AA or AD. Events were obtained by linking data to the Inpatient Register and the Cause of Death register.

Statistical Analysis

The cumulative incidence of AA and AD, as well as subsequent mortality after hospitalization for AA and AD, was estimated using Kaplan-Meier estimates. It was compared between T2DM and CS groups using Cox regression models containing variables that captured sex, age, preexisting conditions, treatment, and socioeconomic variables, which were based on virtually perfect data.

Time updated observations of clinical characteristics from the NDR were evaluated as risk factors for AA and AD using a Cox regression model in which missing values were imputed with the last value carried forward.

Survival after hospitalization for AA and AD was compared between T2DM and CS groups up to 2 years after the index event using Cox regression models that include sex, age, preexisting conditions, and socioeconomic variables, for which the 2-year cutoff was chosen to ensure that the models met the proportional hazards assumption.

Descriptive statistics are presented in terms of averages with SDs and counts with percentages. Because the analyses are explorative rather than confirmative, no corrections for multiple comparisons were made.

Results

Study Population and Demographic Characteristics

Table 1 presents complete unadjusted baseline data, clinical and demographic characteristics of our study population of 448 319 patients with T2DM and 2 251 015 population-based matched CSs. In both study groups, mean ages (65±12 years) and sex distribution (45.6% women) were similar. However, the control group was more often born in Sweden and married and had a higher frequency of college degrees than the T2DM group. The patients with T2DM were more likely to have a history of coronary heart disease, stroke, atrial fibrillation, cardiovascular disease, psychiatric disorders, hyperglycemia, or renal complications. There was no greater difference in the frequency of Marfan syndrome or Ehler-Danlos syndrome between the groups, and the absolute numbers were low. Thus, these conditions were excluded from the main analyses. Mean follow-up time for the patients with T2DM was 7.0 years, as opposed to 7.2 years for the matched controls (Table 2).

Risk of AA or AD

The number of events (hospitalization for AA and AD and number of deaths) and incidence rates are presented in Table 2. During follow-up, there were 2878 cases of AA among patients with T2DM as opposed to 16 740 cases among CSs. For individuals with T2DM, the unadjusted incidence rate of AA was 80.4 per 100 000 person-years as opposed to 93.3 per 100 000 person-years in the control group. The number of deaths was 119 600 among the T2DM group and 482 064 among the CS group. The Kaplan-Meier curve shows crude cumulative incidence rates for AA and AD during follow-up (Figures 1 and 2).

Complete data from the regression analysis are presented in Table 3. There was significantly reduced risk of AA among patients with T2DM compared with CSs (hazard ratio [HR],

Table 1. Baseline Characteristics for Individuals With T2DM and Matched CSs*

Characteristics	T2DM Group (n=448 319)	CS Group (n=2 251 015)
Age, y	65.0 (12.6)	65.0 (12.6)
Sex		
Female	204 377 (45.6)	1 026 640 (45.6)
Male	243 942 (54.4)	1 224 375 (54.4)
Marital status		
Married	237 851 (53.1)	1 248 324 (55.5)
Separated	74 013 (16.5)	356 247 (15.8)
Single	69 984 (15.6)	337 284 (15.0)
Widowed	66 471 (14.8)	309 058 (13.7)
Educational level		
Compulsory school (≤9 y)	191 334 (42.7)	811 325 (36.0)
Upper secondary school (9–12 y)	176 285 (39.3)	870 002 (38.6)
College/university (>12 y)	70 024 (15.6)	529 485 (23.5)
Country of birth		
Sweden	367 900 (82.1)	1 971 495 (87.6)
Rest of world	80 419 (17.9)	279 520 (12.4)
History of comorbidities		
Psychiatric disorders	13 346 (3.0)	43 587 (1.9)
Coronary heart disease	73 995 (16.5)	184 337 (8.2)
Acute myocardial infarction	39 386 (8.8)	92 874 (4.1)
Stroke	28 677 (6.4)	90 478 (4.0)
Cardiovascular disease	63 469 (14.2)	171 886 (7.6)
Atrial fibrillation	31 080 (6.9)	98 839 (4.4)
Renal complications	952 (0.2)	2726 (0.1)
DM complications (hyperglycemia)	5762 (1.3)	640 (0.0)
Dementia	2216 (0.5)	21 830 (1.0)
Marfan syndrome	3 (0.0)	22 (0.0)
Ehler-Danlos syndrome	18 (0.0)	46 (0.0)
Gastric bypass	319 (0.1)	597 (0.0)

Data are presented as means and 1 SD or number and frequency (%). The number of patients in variables with missing data were as follows: marital status (102 in both groups) and educational level (10 676 vs 40 203). CS indicates control subject; and T2DM, type 2 diabetes mellitus.
*Statistical analyses were performed on data, including 448 319 patients with T2DM and 2 251 015 CSs.

0.72; 95% confidence interval [CI], 0.68–0.76; $P<0.0001$). In the regression analysis, we also noted other significant risk factors for AA, including male sex (HR, 3.36; 95% CI, 3.18 to −3.55; $P<0.0001$), hypertension (HR, 1.59; 95% CI, 1.50 to −1.68; $P<0.0001$), dyslipidemia (HR, 1.37; 95% CI, 1.35–1.47; $P<0.0001$), and age (risk/year) (HR, 1.06, 95% CI, 1.06 to −1.07; $P<0.0001$).

During follow-up, there were 200 hospitalizations attributable to AD among patients with T2DM as opposed to 2019 among CSs. The unadjusted incidence rate of AD was 5.6 per 100 000 person-years among patients with T2DM and 11.2 per 100 000 person-years among CSs. The Cox regression estimated a significantly lower risk of AD among the T2DM group than the CS group (HR, 0.53; 95% CI, 0.42–0.65; $P<0.0001$). In the regression analysis, other significant risk factors for AD were male sex (HR, 1.83; 95% CI, 1.58–2.11; $P<0.0001$), hypertension (HR, 1.77; 95% CI, 1.51–2.07; $P<0.0001$), and age (risk/year) (HR, 1.03; 95% CI, 1.03–1.04; $P<0.0001$).

Survival After AA and AD

Survival after hospitalization for AA and AD was followed up until the 2-year cutoff to meet statistical requirements.

Table 2. Follow-Up Period, Number of Events Entered, and Crude Incidence Rates for AA and AD Among Patients With T2DM and Matched CSs

Events	T2DM Group (n=448 319)	CS Group (n=2 251 015)
AA	2878 (80.4)	16 740 (93.3)
AD	200 (5.6)	2019 (11.2)
Deaths	119 600	482 064
Follow-up, y		
Mean	7 (3.59)	7.2 (3.79)
Median	6.5 (4.32–9.23)	6.6 (4.41–9.56)

Values are given as numbers, incidence rate (incidence per 100 000 person-years), means and 1 SD, and median and interquartile range. AA indicates aortic aneurysm; AD, aortic dissection; CS, control subject; and T2DM, type 2 diabetes mellitus.

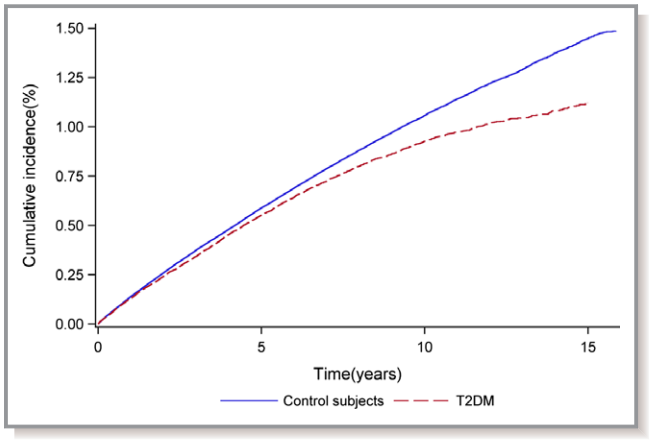

Figure 1. A Kaplan-Meier survival curve presenting unadjusted cumulative incidence rate of aortic aneurysm in individuals with type 2 diabetes mellitus (T2DM) vs population-based matched control subjects. Crude incidence rates were calculated as events per 100 000 person-years.

Unadjusted survival rates with estimated 95% CIs are presented in Table 4. Patients with T2DM had higher unadjusted survival rates than CSs after hospitalization for AA after 3 months, 1 year, and 2 years. Survival rates for T2DM were as follows: after 3 months, 84.20 (95% CI, 82.93–85.38); after 1 year, 74.74 (95% CI, 73.25–76.17); and after 2 years, 66.70 (95% CI, 65.08–68.26). The corresponding rates for CS were as follows: after 3 months, 80.89 (95% CI, 80.33–81.44); after 1 year, 71.67 (95% CI, 71.04–72.30); and after 2 years, 64.21 (95% CI, 63.53–64.88). There were also higher unadjusted survival rates after AD among patients with T2DM than CSs after 3 months, 1 year, and 2 years. Survival rates after hospitalization for AD among patients with T2DM were as follows: after 3 months, 77.86 (95% CI, 72.43–82.35); after 1 year, 73.80 (95% CI, 68.13–78.62); and after 2 years, 67.02 (95% CI, 61.05–72.28). The corresponding rates for CS were as follows: after 3 months, 72.98 (95% CI, 71.17–74.70); after 1 year, 68.49 (95% CI, 66.60–70.30); and after 2 years, 62.94 (95% CI, 60.98–64.83).

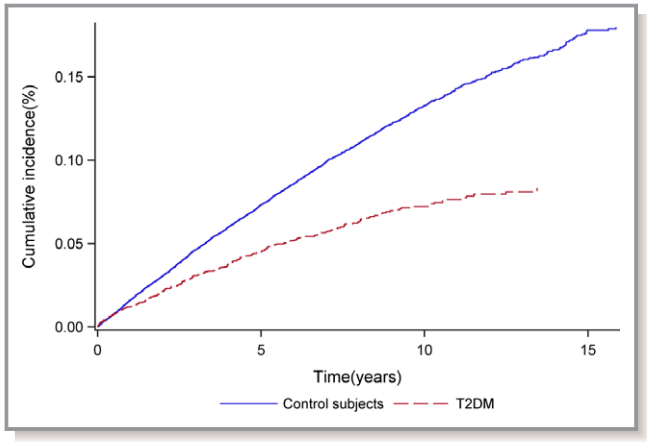

Figure 2. A Kaplan-Meier survival curve presenting unadjusted cumulative incidence rate of aortic dissections in individuals with type 2 diabetes mellitus (T2DM) vs population-based matched control subjects. Crude incidence rates were calculated as events per 100 000 person-years.

Among patients with T2DM, crude mortality rates were 16.7 per 100 person-years after hospitalization for AA and 15.7 per 100 person-years after hospitalization for AD. The corresponding figure for controls was 16.8 per 100 person-years after hospitalization for either AA or AD. We performed a regression analysis that showed a significantly adjusted risk reduction for mortality after hospitalization for AA (HR, 0.88; 95% CI, 0.82–0.94; $P<0.001$) and unaltered risk (HR, 1.07; 95% CI, 0.85–1.34; $P=0.586$) for mortality after AD up to 2 years among the T2DM group compared with the CS group.

A Kaplan-Meier curve demonstrates crude rates of survival after hospitalization for AA or AD (Figures 3 and 4).

Ancillary Analysis

An ancillary regression analysis on the same study cohort as in Table 3 was performed on hospitalization for subgroups of AA (thoracic AA, thoracoabdominal AA, abdominal AA, and unspecified AA). This was done to compare estimates with the results generated from Table 3 (all locations of AA merged into 1 AA group) to increase sensitivity. The ancillary analysis indicated significantly decreased risks of hospitalization for thoracic, abdominal, and unspecified AA in patients with DM compared with CSs, with the difference in estimates slightly more prominent in the ancillary analysis. The risk of hospitalization for thoracoabdominal AA was unaltered between the study groups. See Table S2 and Figures S1 through S4 for more detailed data. A corresponding ancillary analysis could not be performed on subgroups of AD, however, because the few events registered lead to poor statistical significance.

Table 3. Risk of AA and AD and Adjusted HRs for Other Studied Outcomes Among Individuals With T2DM and Matched CSs

Characteristics	AA Group	AD Group
Subjects		
T2DM vs CS	0.72 (0.68–0.76)*†	0.53 (0.42–0.65)*†
Sex		
Male vs female	3.36 (3.18–3.55)*	1.83 (1.58–2.11)*
History of comorbidities		
Stroke	1.36 (1.16–1.58)*	0.94 (0.41–2.20)
Cardiovascular disease	0.94 (0.79–1.12)	1.43 (0.58–3.50)
Coronary heart disease	1.34 (1.24–1.44)*	0.90 (0.66–1.23)
Acute myocardial infarction	1.18 (1.00–1.40)*	0.87 (0.36–2.11)
Atrial fibrillation	0.94 (0.87–1.02)	1.05 (0.79–1.14)
Renal complications	1.69 (1.10–2.60)*	NS
Psychiatric disorders	0.95 (0.81–1.11)	1.61 (1.10–2.36)*
Hypertension	1.59 (1.50–1.68)*	1.77 (1.51–2.07)*
DM complication (hyperglycemia)	1.01 (0.63–1.63)	0.99 (0.14–7.08)
Dementia	0.43 (0.31–0.60)*	0.14 (0.02–0.98)*
Cancer	1.11 (1.03–1.20)*	1.04 (0.81–1.32)
Gastric bypass	1.51 (0.38–6.04)	NA
Use of medications		
Anticoagulation therapy	1.15 (1.07–1.23)*	0.86 (0.66–1.12)
Lipid-lowering medication	1.37 (1.35–1.47)*	0.89 (0.74–1.08)
ASA	1.32 (1.25–1.40)*	0.95 (0.78–1.15)
Age (risk/year)	1.06 (1.06–1.07)*	1.03 (1.03–1.04)*
Country of birth		
Rest of World vs Sweden	0.98 (0.91–1.05)	1.00 (0.82–1.23)
Marital status		
Married vs single	1.22 (1.12–1.32)*	1.27 (1.01–1.60)*
Separated vs single	1.55 (1.42–1.70)*	1.39 (1.07–1.81)*
Widowed vs single	1.22 (1.10–1.34)*	1.19 (0.88–1.60)
Educational level		
Upper secondary school vs elementary school	0.88 (0.83–0.92)*	0.99 (0.85–1.15)
College/university vs elementary school	0.63 (0.59–0.68)*	0.88 (0.73–1.06)

vs = versus. Risk of outcomes is presented as adjusted hazard ratio (95% confidence interval) unless otherwise stated. Subjects with previous AA and AD were excluded from the analysis. AA indicates aortic aneurysm; AD, aortic dissection; ASA, acetylsalicylic acid; CS, control subject; HR, hazard ratio; NA, not applicable; NS, not significant; and T2DM, type 2 diabetes mellitus.

*$P<0.05$.

†Adjusted for variables including sex, stroke, cardiovascular disease, coronary heart disease, acute myocardial infarction, atrial fibrillation, renal complications, mental disorders, hypertension, DM complications, dementia, cancers, gastric bypass, use of anticoagulation therapy, lipid-lowering drugs, ASA, country of birth, marital status, and educational level.

Table 4. Unadjusted Estimated Survival After 3 Months, 1 Year, 2 Years, and 3 Years Among Individuals With T2DM, Compared With Matched CSs, After an Event of AA or AD, With 95% CIs

End Point	Time, y	T2DM Group	CS Group
AA	0.25	84.20 (82.93–85.38)	80.89 (80.33–81.44)
II	1	74.74 (73.25–76.17)	71.67 (71.04–72.30)
	2	66.70 (65.08–68.26)	64.21 (63.53–64.88)
	3	59.18 (57.45–60.86)	57.88 (57.16–58.58)
AD	0.25	77.86 (72.43–82.35)	72.98 (71.17–74.70)
II	1	73.80 (68.13–78.62)	68.49 (66.60–70.30)
	2	67.02 (61.05–72.28)	62.94 (60.98–64.83)
	3	64.00 (57.89–69.46)	57.61 (55.57–59.59)

Data are given as hazard ratio (HR; 95% CI). Regression analysis found adjusted relative risk reduction of 12% (HR, 0.88; 95% CI, 0.82–0.94; $P<0.0001$) for mortality after AA, and unaltered risk (HR, 1.07; 95% CI, 0.85–1.34; $P=0.5859$) for mortality after AD, among the T2DM group compared with CSs, up to 2 years. AA indicates aortic aneurysm; AD, aortic dissection; CI, confidence interval; CS, control subject; and T2DM, type 2 diabetes mellitus.

Discussion

This nationwide observational study cohort of nearly 3 million people contains demographic data and clinical characteristics for patients with T2DM hospitalized for AA and AD, strengthening the hypothesis of a general long-term risk reduction of hospitalization for AA and AD among patients with T2DM compared with CSs from the general population. It also documents significantly lower risk of 2-year all-cause mortality after hospitalization for AA among patients with T2DM compared with CSs.

Interest in the relationship between AA and T2DM has rapidly increased since it was first hypothesized by Lederle et al[23] in 1997 in the Aneurysm Detection and Management Veterans Affairs Cooperative Study Group. The main hypothesis is an inverse risk of AA among patients with T2DM, both thoracic AA[5,8] and abdominal AA.[2,23–25] One of the largest studies to date, a longitudinal Taiwanese effort, based on inpatient/insurance registers, found 15% lower incidence rates of AA among patients with T2DM than controls (15% lower; 3.85 versus 4.51 per 100 000 person-years; HR, 0.65; 95% CI, 0.56–0.74; $P<0.001$).[14] A meta-analysis with large prevalence data showed similar findings on abdominal AA,[26] whereas we report a general risk reduction of hospitalization for AA among patients with T2DM compared with CSs.

The healthy men study found that a reduced risk of AA was correlated with the follow-up period (DM duration) among patients with DM, with the odds ratio decreasing from 0.50 in the 3- to 5-year follow-up to 0.37 after 12 years.[27] It has also been suggested that the positive effect of T2DM on the risk of AA is enhanced if glycemic control is poor.[8,14] Given our study

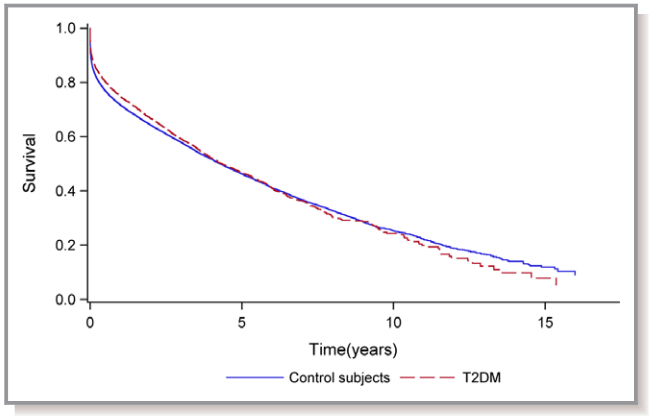

Figure 3. A Kaplan-Meier survival curve presenting unadjusted estimated survival among individuals with type 2 diabetes mellitus (T2DM) vs population-based matched control subjects (CSs) after an event of aortic aneurysm (AA). Crude incidence rates were calculated as events per 100 person-years. Regression analysis was performed on the data set. It found significant adjusted risk reduction of 12% (hazard ratio [HR], 0.88; 95% confidence interval (CI), 0.82–0.94; $P<0.0001$) for mortality after AA, and unaltered risk (HR, 1.07; 95% CI, 0.85–1.34) for mortality after aortic dissection, up to 2 years, among the T2DM group, compared with CSs.

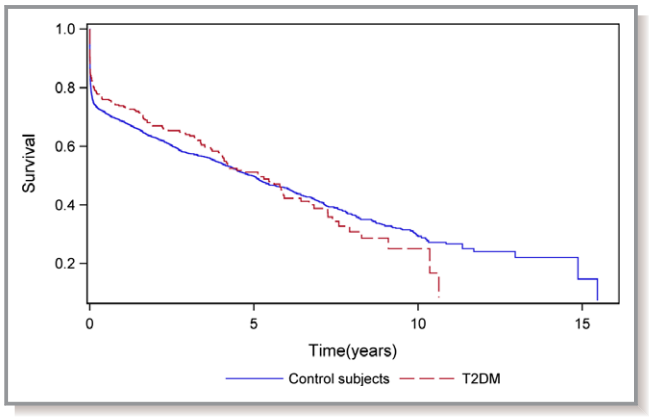

Figure 4. A Kaplan-Meier survival curve presenting unadjusted estimated survival among individuals with type 2 diabetes mellitus (T2DM) vs population-based matched control subjects (CSs) after an event of aortic dissection (AD). Crude incidence rates were calculated as events per 100 person-years. Regression analysis was made on the data set. It found significant adjusted risk reduction of 12% (hazard ratio [HR], 0.88; 95% confidence interval (CI), 0.82–0.94; $P<0.0001$) for mortality after aortic aneurysm, and unaltered risk (HR, 1.07; 95% CI, 0.85–1.34) for mortality after AD, up to 2 years, among the T2DM group compared with CSs.

design, we aimed to explore the association between T2DM and aortic diseases, independent of glycemic control and mean glycated hemoglobin. Also, we did not observe whether the protective effect of T2DM was correlated to DM duration. Future studies should examine this relationship. The incidence rates of AA and AD among CSs were similar to previous observational studies,[28–30] which reinforces the validity of our data.

Researchers have recently broadened the field and begun to examine the association between aortic diseases (both AA and AD) and DM.[8,31] Our study was designed accordingly. About the risk of AD, a US epidemiological case-control study performed by Prakash et al found a 40% to 80% risk reduction of AD, primarily thoracic, among the T2DM group compared with matched controls.[8] Similar associations were found in a small single-center study.[32] We report a general risk reduction of hospitalization for AD among patients with T2DM compared with CSs.

The previously described studies may separately have some flaws, such as study design (case-control), method (self-reported AA and AD), small cohorts, and short follow-up periods. Nevertheless, all of them show the inverse risk of aortic diseases among the T2DM group.[33] Our longitudinal observational study strongly increases the likelihood of the observed associations. The NDR and similar quality registers should be used in the future to explore the association further.

The novel findings presented in the study suggest that patients with T2DM have a significantly reduced risk of short-term mortality after hospitalization for AA compared with CSs. The reason is unclear, but may partly be that individuals with T2DM are protected from AA expansion and rupture, and consequently AA-related death. The unadjusted short-term mortality assessment after AD hospitalization found higher survival rates up to 2 years after AD among the T2DM group than the CS group. The statistically insignificant risk elevation for mortality after AD (with a point estimate of 1.07, close to 1.0) together with beneficial unadjusted survival rates should not be interpreted as damaging effects of T2DM on mortality after hospitalization for AD in patients with DM. Perhaps T2DM also has protective effects on mortality after AD. Our results could stem from an insufficient number of events entered, resulting in poor statistical power. It is also well known that patients with DM have a higher risk of cardiovascular morbidity/mortality than subjects without DM.[34] Our patients with T2DM used statins and antihypertensive medication more frequently than CSs, resulting in better risk factor control.[35] However, our large study cohort and adjustments in analysis indicate that it is not the main explanation. The mortality regression analysis will be performed again in the future when more events have been obtained, stratifying all-cause mortality into aortic disease mortality, cardiovascular mortality, and cancer mortality, enabling the detection of DM effect on aortic disease mortality. In the meantime, we are confident of short-term protection from mortality after AA in patients with T2DM.

We document long-term crude equalized or even increased risk of mortality after hospitalization for both AA and AD

among patients with T2DM compared with CSs. Prolonged DM duration, with or without hyperglycemia, and other DM complications might perhaps eliminate the observed positive short-term effects.[12,18,36,37]

The mechanisms of the observed associations are still unknown. Biological alteration of the aortic wall in patients with DM may be one explanation. DM may delay enlargement of the aorta through metabolic pathways, which reduces the inflammatory response by the aortic wall.[23,24] Glycemia, even if well regulated, may armor the aortic wall through stronger glycated cross-links in vascular extracellular matrices.[23,24,38] Hindered aortic root dilatation among patients with T2DM may also play a role in the observed associations. A Chinese study of 109 patients with T2DM found less prevalence of aortic dilatation than matched controls, using 2-dimensional echocardiography.[39]

Hypertension and dyslipidemia are strong risk factors associated with the development of AA and AD.[2,6,14,23,24] Together with T2DM, they are strongly associated with increased risk of cardiovascular comorbidity and mortality.[15,36,37] Thus, these patients may be offered more frequent appointments at primary health care clinics, stricter blood pressure controls, and treatment for dyslipidemia.[40] Use of antihypertensive medication, especially angiotensin-converting enzyme inhibitors, has been suggested to slow progression of formation of AA, but the topic is still highly debated and no scientific consensus exists.[41]

Being normotensive with antihypertensive treatment is not the same as having normal blood pressure. Despite drug treatment, systemic inflammation attributable to hypertension is still present. This could be further strengthened by the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study, documenting the hypothesis that intensive therapy for high blood pressure is not justified compared with standard targets.[42] The same may be true of dyslipidemia. Nevertheless, we found an inverse risk of AA and AD and reduced short-term risk of mortality after AA among patients with T2DM compared with CSs. Using antihypertensive and lipid-lowering medication is a mediating factor and may have affected our results to some extent, but the large study cohort and the adjustments made in regression analysis indicate it is not the main explanation. Also, thorough follow-up of T2DM and hypertension in primary health care has no effect when it comes to predicting them.

To sum up its strengths, our study contained one of the largest study populations to date with nationwide valid data on DM, comorbidities, and outcomes (both AA and AD) and has a long mean follow-up period. Population-based CSs functioned as a comparison group, with 5:1 matched controls, resulting in high statistical power. Randomized clinical trials are the gold standard method for explaining causality of observed findings, whereas genetics (mendelian randomization) is a comparable method. For this study, it would be unethical and impossible to conduct a randomized clinical trial. In many cases, observational studies are equivalent to randomized clinical trials with respect to generating results,[43] but not all agree.[44] Longitudinal observational studies may be the best way for now to establish relationships between aortic diseases and T2DM.

Some limitations are worth considering. It is a nigh unto impossible task to completely overcome residual confounders in observational studies. However, we tried to identify and adjust for the most important ones. We refrained from adjustment when changes in comorbidities (hypertension and dyslipidemia) occurred during follow-up, assessing comorbidities only at baseline. Otherwise, we may have affected a possible mediating factor of our observations. Information about DM duration before study start was missing. Subjects were followed up from baseline until an outcome occurred. If some protective effect of AA and AD among patients with T2DM is associated with DM duration, adjustment would have generated more beneficial observations than we found. Moreover, no stratifications of blood pressure levels were performed to determine which subjects were near normotensive with treatment and which ones had border hypertension without treatment. This will be performed again in a subsequent study.

What other possible unmeasured confounders could have affected our results? Smoking is a strong factor that may attribute to formation of aortic diseases, including AA.[2,4,5,8] Because the longitudinal integration database for health insurance and job market studies lacks data about smoking history, these data could not be retrieved among our CSs, which is a major limitation. The Institute of Public Health and Welfare is one of few databases containing data on smoking history, but reporting is voluntary and coverage is oscillating. The institute reported that ≈8% to 10% of all Swedes in age groups of 16 to 84 years smoke. However, almost 20% of all Swedish men and women aged 45 to 64 years were smokers, and in adjacent age groups (ages: 16–29, 30–44, and 65–84 years), 8% to 12% of Swedes were smokers.[45] One other study showed similar results.[46] Given our large study population and lack of upper age limitation for study inclusion, it is likely that number of smokers among our CSs is between the previously mentioned percentages. Smoking is assessed in the NDR: 16% of our patients with T2DM were smokers. On this basis, smoking might have had an intermediate or a smaller impact on our observations but is improbable to be a plausible explanation for the observed results. However, this is speculative and the lack of data on smoking hampers our evaluation of the effect of T2DM on the risk of formation of aortic diseases. Moreover, the regression analysis found an insignificant difference in the number of gastric bypass procedures between the study groups, indicating no

difference in morbid obesity and thus having no effect on our observed findings. Connective tissue disorders, such as Marfan and Ehler-Danlos syndromes, are also risk factors for aortic diseases.[6,9] We found a small absolute number of cases in both study groups. They were not included in the analysis because it would not have altered the finding and would have skewed our statistical power.

In conclusion, this nationwide, observational, longitudinal cohort study found that patients with T2DM have a significantly reduced risk of hospitalization for AA and AD compared with CSs, as well as significantly reduced short-term risk of mortality after hospitalization for AA. Data suggest that T2DM alters the aortic tissue through glycemic cross-links, creating a protective effect towards stabilization of the aorta, preventing aortic dilatation, aneurysm growth, and rupture.

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Disclosures

None.

References

1. Johansson G, Markström U, Swedenborg J. Ruptured thoracic aortic aneurysms: a study of incidence and mortality rates. *J Vasc Surg*. 1995;21:985–988.
2. Moll FL, Powell JT, Fraedrich G, Verzini F, Haulon S, Waltham M, van Herwaarden JA, Holt PJE, van Keulen JW, Rantner B, Schlösser FJV, Setacci F, Ricco J-B. Management of abdominal aortic aneurysms clinical practice guidelines of the European society of vascular surgery. *Eur J Vasc Endovasc Surg*. 2011;41(suppl 1):S1–S58.
3. Hagan PG, Nienaber CA, Isselbacher EM, Bruckman D, Karavite DJ, Russman PL, Evangelista A, Fattori R, Suzuki T, Oh JK, Moore AG, Malouf JF, Pape LA, Gaca C, Sechtem U, Lenferink S, Deutsch HJ, Diedrichs H, Marcos y Robles J, Llovet A, Gilon D, Das SK, Armstrong WF, Deeb GM, Eagle KA. The International Registry of Acute Aortic Dissection (IRAD): new insights into an old disease. *JAMA*. 2000;283:897–903.
4. Pape LA, Tsai TT, Isselbacher EM, Oh JK, O'Gara PT, Evangelista A, Fattori R, Meinhardt G, Trimarchi S, Bossone E, Suzuki T, Cooper JV, Froehlich JB, Nienaber CA, Eagle KA. Aortic diameter > or = 5.5 cm is not a good predictor of type A aortic dissection: observations from the International Registry of Acute Aortic Dissection (IRAD). *Circulation*. 2007;116:1120–1127.
5. Landenhed M, Engström G, Gottsäter A, Caulfield MP, Hedblad B, Newton-Cheh C, Mellander O, Smith JG. Risk profiles for aortic dissection and ruptured or surgically treated aneurysms: a prospective cohort study. *J Am Heart Assoc*. 2015;4:e001513. DOI: 10.1161/JAHA.114.001513.
6. Golledge J, Eagle KA. Acute aortic dissection. *Lancet*. 2008;372:55–66.
7. Bhak RH, Wininger M, Johnson GR; Aneurysm Detection and Management (ADAM) Study Group. Factors associated with small abdominal aortic aneurysm expansion rate. *JAMA Surg*. 2015;150:44–50.
8. Prakash SK, Pedroza C, Khalil YA, Milewicz DM. Diabetes and reduced risk for thoracic aortic aneurysms and dissections: a nationwide case-control study. *J Am Heart Assoc*. 2012;1:e000323. DOI: 10.1161/JAHA.111.000323.
9. Nienaber CA, Eagle KA. Aortic dissection: new frontiers in diagnosis and management: part I: from etiology to diagnostic strategies. *Circulation*. 2003;108:628–635.
10. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care*. 1993;16:434–444.
11. Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes Res Clin Pract*. 2011;94:311–321.
12. Gæde P, Vedel P, Larsen N, Jensen GVH, Parving H-H, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med*. 2003;348:383–393.
13. Lederle FA, Noorbaloochi S, Nugent S, Taylor BC, Grill JP, Kohler TR, Cole L. Multi-centre study of abdominal aortic aneurysm measurement and enlargement. *Br J Surg*. 2015;102:1480–1487.
14. Tsai CL, Lin CL, Wu YY, Shieh DC, Sung FC, Kao CH. Advanced complicated diabetes mellitus is associated with a reduced risk of thoracic and abdominal aortic aneurysm rupture: a population-based cohort study. *Diabetes Metab Res Rev*. 2015;31:190–197.
15. Pasterkamp G. Methods of accelerated atherosclerosis in diabetic patients. *Heart*. 2013;99:743–749.
16. Eliasson B, Gudbjörnsdottir S. Diabetes care: improvement through measurement. *Diabetes Res Clin Pract*. 2014;106(suppl 2):S291–S294.
17. Annual report 2013. Sweden: Swedish National Diabetes Register (NDR); 2013. Available at: http://www.ndr.nu. Accessed March 21, 2017.
18. Lind M, Olsson M, Rosengren A, Svensson AM, Bounias I, Gudbjörnsdottir S. The relationship between glycaemic control and heart failure in 83,021 patients with type 2 diabetes. *Diabetologia*. 2012;55:2946–2953.
19. Lind M, Svensson AM, Kosiborod M, Gudbjörnsdottir S, Pivodic A, Wedel H, Dahlqvist S, Clements M, Rosengren A. Glycemic control and excess mortality in type 1 diabetes. *N Engl J Med*. 2014;371:1972–1982.
20. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, Heurgren M, Olausson PO. External review and validation of the Swedish national inpatient register. *BMC Public Health*. 2011;11:450.
21. Wettermark B, Hammar N, Fored CM, Leimanis A, Olausson PO, Bergman U, Persson I, Sundström A, Westerholm B, Rosén M. The new Swedish Prescribed Drug Register: opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf*. 2007;16:726–735.
22. Merlo J, Lindblad U, Pessah-Rasmussen H, Hedblad B, Rastam J, Isacsson SO, Janzon L, Råstam L. Comparison of different procedures to identify probable cases of myocardial infarction and stroke in two Swedish prospective cohort studies using local and national routine registers. *Eur J Epidemiol*. 2000;16:235–243.
23. Lederle FA, Johnson GR, Wilson SE, Chute EP, Littooy FN, Bandyk D, Krupski WC, Barone GW, Acher CW, Ballard DJ. Prevalence and associations of abdominal aortic aneurysm detected through screening. *Ann Intern Med*. 1997;126:441–449.
24. Golledge J, Karan M, Moran CS, Muller J, Clancy P, Dear AE, Norman PE. Reduced expansion rate of abdominal aortic aneurysms in patients with diabetes may be related to aberrant monocyte-matrix interactions. *Eur Heart J*. 2008;29:665–672.
25. Wang L, Djousse L, Song Y, Akinkuolie AO, Matsumoto C, Manson JE, Gaziano JM, Sesso HD. Associations of diabetes and obesity with risk of abdominal aortic aneurysm in men. *J Obes*. 2017;2017:3521649.
26. De Rango P, Farchioni L, Fiorucci B, Lenti M. Diabetes and abdominal aortic aneurysms. *Eur J Vasc Endovasc Surg*. 2014;47:243–261.
27. Le MT, Jamrozik K, Davis TM, Norman PE. Negative association between infrarenal aortic diameter and glycaemia: the Health in Men Study. *Eur J Vasc Endovasc Surg*. 2007;33:599–604.
28. Olsson C, Thelin S, Stahle E, Ekbom A, Granath F. Thoracic aortic aneurysm and dissection: increasing prevalence and improved outcomes reported in a nationwide population-based study of more than 14000 cases from 1987 to 2002. *Circulation*. 2006;114:2611–2618.
29. Howard DP, Sideso E, Handa A, Rothwell PM. Incidence, risk factors, outcome and projected future burden of acute aortic dissection. *Ann Cardiothorac Surg*. 2014;3:278–284.
30. Singh K, Bonaa KH, Jacobsen BK, Bjork L, Solberg S. Prevalence of and risk factors for abdominal aortic aneurysms in a population-based study: the Tromsø Study. *Am J Epidemiol*. 2001;154:236–244.
31. He X, Liu X, Liu W, Wang B, Liu Y, Li Z, Wang T, Tan R, Gao B, Zeng H. Association between diabetes and risk of aortic dissection: a case-control study in a Chinese population. *PLoS One*. 2015;10:e0142697.

32. Theivacumar NS, Stephenson MA, Mistry H, Valenti D. Diabetics are less likely to develop thoracic aortic dissection: a 10-year single-center analysis. *Ann Vasc Surg*. 2014;28:427–432.
33. Nienaber CA. Diabetes mellitus and thoracic aortic disease: are people with diabetes mellitus protected from acute aortic dissection? *J Am Heart Assoc*. 2012;1:e001404. DOI: 10.1161/JAHA.112.001404.
34. Rawshani A, Rawshani A, Franzén S, Eliasson B, Svensson AM, Miftaraj M, McGuire DK, Sattar N, Rosengren A, Gudbjörnsdottir S. Mortality and cardiovascular disease in type 1 and type 2 diabetes. *N Engl J Med*. 2017;376:1407–1418.
35. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ*. 2002;324:71–86.
36. Kurukulasuriya LR, Sowers JR. Therapies for type 2 diabetes: lowering HbA1c and associated cardiovascular risk factors. *Cardiovasc Diabetol*. 2010;9:45.
37. Skyler JS, Bergenstal R, Bonow RO, Buse J, Deedwania P, Gale EA, Howard BV, Kirkman MS, Kosiborod M, Reaven P, Sherwin RS; American Diabetes Association, American College of Cardiology Foundation, American Heart Association. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. *Circulation*. 2009;119:351–357.
38. Dua MM, Miyama N, Azuma J, Schultz GM, Sho M, Morser J, Dalman R. Hyperglycemia modulates plasminogen activator inhibitor-1 expression and aortic diameter in experimental aortic aneurysm disease. *Surgery*. 2010;148:429–435.
39. Chen XF, Wang JA, Lin XF, Tang LJ, Yu WF, Chen H, Xie XJ, Jiang JJ, Peng XH. Diabetes mellitus: is it protective against aortic root dilatation? *Cardiology*. 2009;112:138–143.
40. Snow R, Humphrey C, Sandall J. What happens when patients know more than their doctors? Experiences of health interactions after diabetes patient education: a qualitative patient-led study. *BMJ Open*. 2013;3:e003583.
41. Thompson A, Cooper JA, Fabricius M, Humphries SE, Ashton HA, Hafez H. An analysis of drug modulation of abdominal aortic aneurysm growth through 25 years of surveillance. *J Vasc Surg*. 2010;52:55–61.
42. Cushman WC, Evans GW, Byington RP, Goff DC Jr, Grimm RH Jr, Cutler JA, Simons-Morton DG, Basile JN, Corson MA, Probstfield JL, Katz L, Peterson KA, Friedewald WT, Buse JB, Bigger JT, Gerstein HC, Ismail-Beigi F; ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med*. 2010;362:1575–1585.
43. Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. *N Engl J Med*. 2000;342:1878–1886.
44. Pocock SJ, Elbourne DR. Randomized trials or observational tribulations? *N Engl J Med*. 2000;342:1907–1909.
45. Annual report 2016. Sweden: Institute of Common Health and Welfare; 2016. Available at: http://www.folkhalsomyndigheten.se. Accessed January 6, 2017.
46. Forouzanfar MH, Afshin A, Alexander LT. Global, regional, and national comparative risk assessment of 79 behavioral, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388:1659–1724.

SUPPLEMENTAL MATERIAL

Table S1. 9th and 10th revision of International Classification of Diseases Codes (ICD-codes)

Diagnosis	ICD 9 - codes	ICD10 - codes
Coronary Heart Disease (CHD)	410-414	I20-25
Acute Myocardial Infarction (AMI)	410	I21
Stroke	431-434, 436	I61-64
Atrial Fibrillation (AF)	427D	I48
Heart Failure (HF)	428	I50
Marfans Syndrome	759.82	Q87.4
Ehler-Danlos Syndrome	756.83	Q79.6
Dementia		G30.0, G30.1, G30.8, G30.9, F00-F03
Diabetic Complications - Hyperglycemia		E10.0, E10.1, E11.0, E11.1, E12.0, E12.1, E13.0, E13.1, E14.0, E14.1
Cancer	140-208	C00-C97
Renal Complications	V42A, V45B, V56A, V56W	Z94.0-Z49.2, Z99.2
Psychiatric Disorders		F20-29, F30-39

Table S2. Risk for hospitalization of subgroups of aortic aneurysms (AA) and adjuster hazard ratios for other studied outcomes among individuals with type 2 diabetes (T2DM) and matched control subjects (CS).

Characteristics	Thoracic AA	Abdominal AA	Thoracoabdominal AA	Unspecified AA
Subjects				
- T2DM vs CS	0.56 (0.48, 0.65)*†	0.75 (0.70, 0.80) *†	0.92 (0.65, 1.31)†	0.69 (0.59, 0.80) *†
Sex				
- Male vs female	1.94 (1.73, 2.17)*	4.13 (3.86, 4.41) *	1.79 (1.32, 2.42) *	2.62 (2.30, 2.98) *
History of Comorbidities				
- Stroke	0.92 (0.49, 1.71)	1.32 (1.12, 1.56) *	1.53 (0.53, 4.46)	1.90 (1.35, 2.67) *
- Cardio vascular disease (CVD)	1.17 (0.60, 2.27)	1.01(0.83, 1.22)	0.78 (0.23, 2.62)	0.66 (0.44, 0.98) *
- Coronary heart disease (CHD)	0.92 (0.74, 1.14)	1.44 (1.32, 1.56) *	1.34(0.81, 2.22)	1.40 (1.16, 1.68) *
- Acute myocardial infarction (AMI)	0.77 (0.40, 1.47)	1.15 (0.95, 1.38)	1.47 (0.45, 4.80)	1.51 (1.03, 2.20) *
- Atrial fibrillation (AF)	1.06 (0.87, 1.30)	0.92(0.84, 1.00)	0.49 (0.25, 0.97) *	0.99 (0.82, 1.19)
- Renal Complications	0.96 (0.24, 3.86)	1.72(1.05, 2.81) *	7.20 (1.78, 29.15) *	1.04 (0.26, 4.18)
- Psychiatric Disorders	0.80 (0.54, 1.19)	1.01 (0.85, 1.21)	0.45(0.11, 1.82)	1.00 (0.68, 1.45)
- Hypertension	2.13 (1.88, 2.41) *	1.46 (1.37, 1.56) *	2.55 (1.79, 3.63) *	1.84 (1.59, 2.12) *
- Diabetes Complication - hyperglycemia	0.50 (0.07, 3.56)	1.04 (0.61, 1.76)	N/A	1.49 (0.55, 4.00)
- Dementia	0.16 (0.04, 0.64) *	0.47 (0.33, 0.68) *	1.15 (0.28, 4.71) *	0.20 (0.06, 0.62) *
- Cancer	1.03 (0.86, 1.24)	1.11(1.02, 1.21) *	1.05 (0.65, 1.69)	1.19 (1.00, 1.42) *
- Gastric By-pass (Gby-P)	2.62 (0.37, 18.67)	1.15 (0.16, 8.15)	N/A	N/A
Usage of Medications:				

- Anti-coagulation therapy	1.20 (1.01, 1.44) *	1.13 (1.04, 1.22) *	0.85 (0.52, 1.40)	1.28 (1.09, 1.51) *
- Lipid lowering medication	0.99 (0.86, 1.13)	1.50 (1.41, 1.60) *	1.21 (0.86, 1.71)	1.24 (1.08, 1.42) *
- ASA	1.19 (1.03, 1.36) *	1.37 (1.28, 1.46) *	0.97 (0.67, 1.40)	1.34 (1.17, 1.55) *
Age (Risk/Year)	1.04 (1.03, 1.04) *	1.07 (1.06, 1.07) *	1.05 (1.03, 1.07) *	1.07(1.06, 1.08) *
Country of Birth				
- Rest of World vs Sweden	1.10 (0.95, 1.28)	0.94 (0.87, 1.02)	0.86 (0.55, 1.34)	0.98 (0.82, 1.16)
Marital Status:				
- Married vs Single	0.99 (0.83, 1.17)	1.34 (1.21, 1.48) *	1.83(1.00, 3.34) *	1.01 (0.82, 1.23)
- Separated vs Single	1.23 (1.01, 1.49) *	1.72 (1.54, 1.92) *	2.35 (1.22, 4.51) *	1.46 (1.17, 1.83) *
- Widowed vs Single	1.03 (0.83, 1.28)	1.32 (1.17, 1.48) *	1.79 (0.90, 3.57)	1.12 (0.88, 1.42)
Educational Level:				
- Upper secondary school vs elementary school	1.01 (0.90, 1.14) *	0.86 (0.82, 0.91) *	0.74 (0.54, 1.01)	0.81 (0.71, 0.91) *
- College/University vs elementary school	0.86 (0.75, 1.00) *	0.56 (0.52, 0.60) *	0.67 (0.45, 1.00) *	0.66 (0.56, 0.78) *

*= P value < 0.05

†= Adjusted for variables including sex, stroke, CVD, CHD, AMI, AF, renal complications, mental disorders, hypertension, diabetes complications, dementia, cancers, Gby-P, usage of anti-coagulation therapy, lipid lowering drugs, ASA, country of birth, marital status and educational level. VS= reference values when conducting regression analysis. Risk of outcomes are presented as adjusted Hazard ratio, HR, with 95 % confidence intervals (95 % CI) unless otherwise stated. Subjects with previous aortic aneurysm (AA) were excluded from the analysis

Figure S1. A Kaplan-Meier survival curve presenting unadjusted cumulative incidence rate of thoracic aortic aneurysm (AA) in individuals with type 2 diabetes (T2DM) versus population-based matched control subjects (CS).

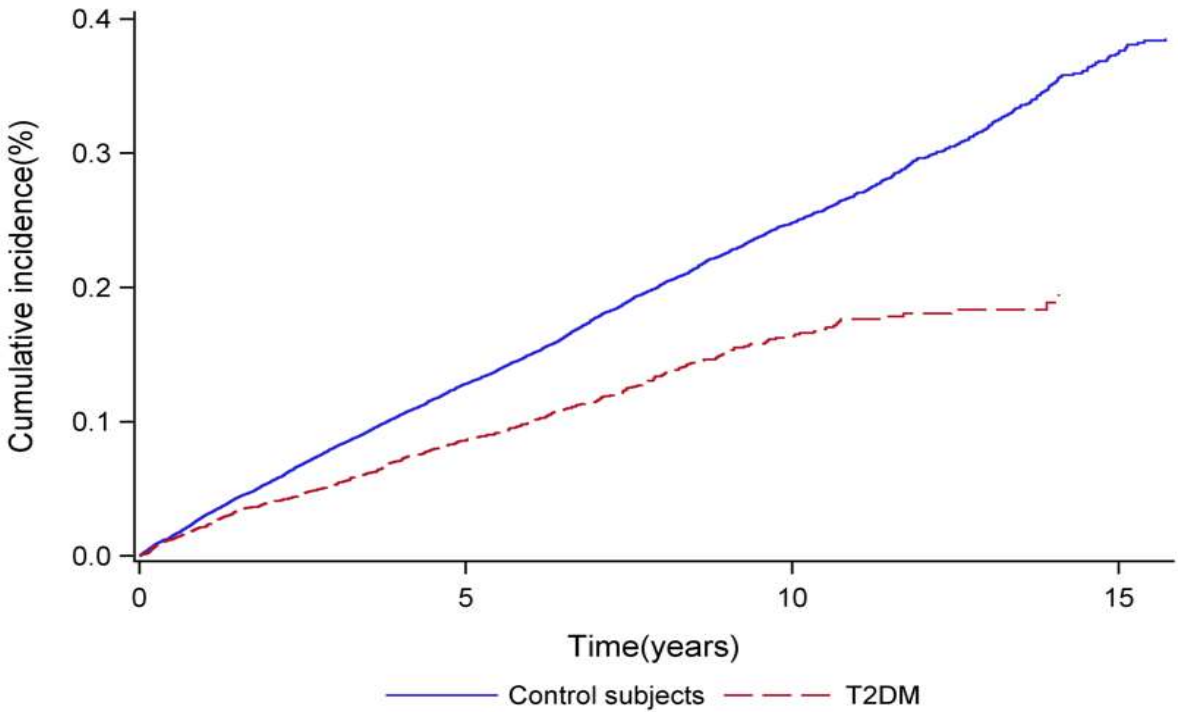

Figure S2. A Kaplan-Meier survival curve presenting unadjusted cumulative incidence rate of thoracoabdominal aortic aneurysm (AA) in individuals with type 2 diabetes (T2DM) versus population-based matched control subjects (CS).

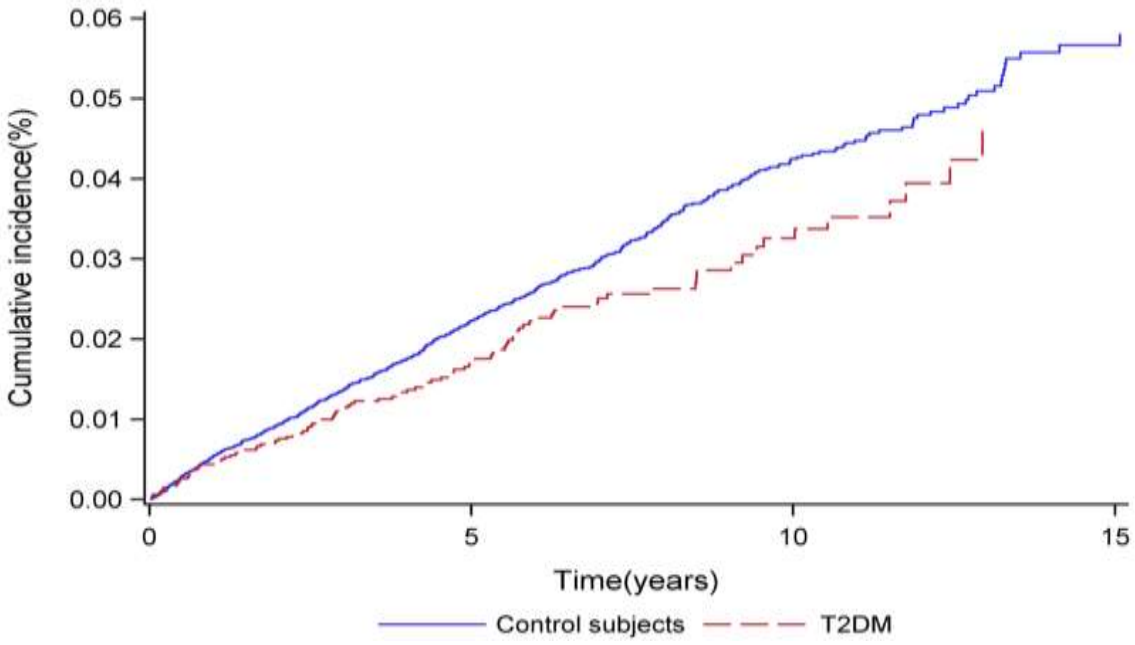

Figure S3. A Kaplan-Meier survival curve presenting unadjusted cumulative incidence rate of abdominal aortic aneurysm (AA) in individuals with type 2 diabetes (T2DM) versus population-based matched control subjects (CS).

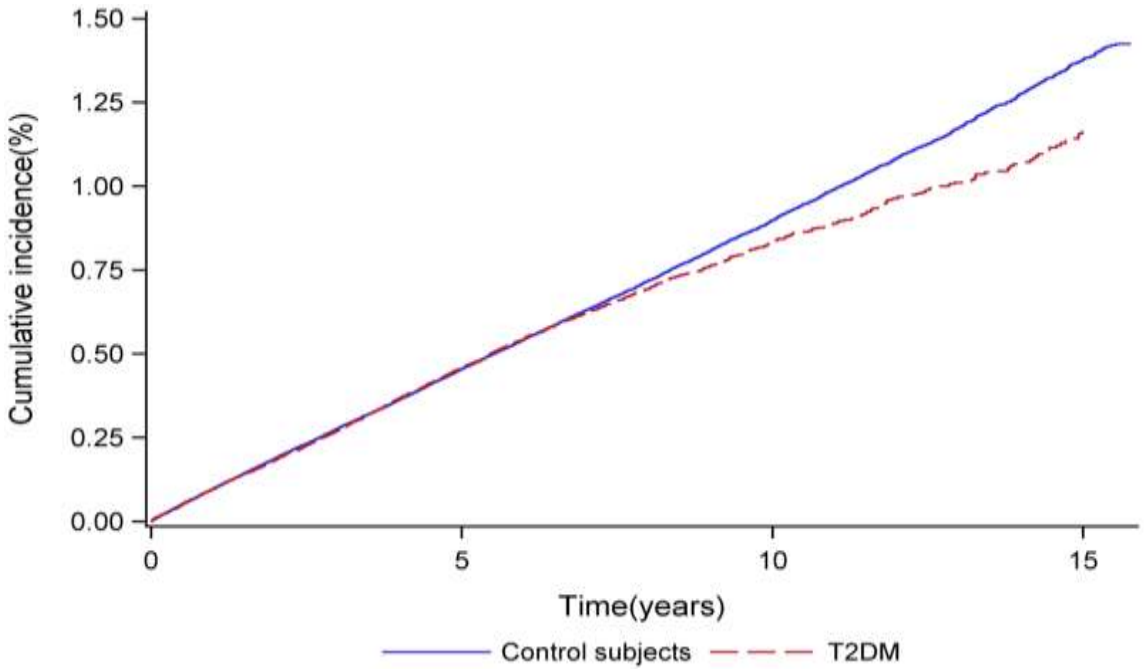

Figure S4. A Kaplan-Meier survival curve presenting unadjusted cumulative incidence rate of unspecified aortic aneurysm (AA) in individuals with type 2 diabetes (T2DM) versus population-based matched control subjects (CS).